Europace (2011) **13**, 1541–1549
doi:10.1093/europace/eur135

The electroanatomical remodelling of the left atrium is related to $CHADS_2/CHA_2DS_2VASc$ score and events of stroke in patients with atrial fibrillation

Jae Hyung Park[1], Boyoung Joung[1], Nak-Hoon Son[2], Jae Min Shim[1], Moon Hyung Lee[1], Chun Hwang[3], and Hui-Nam Pak[1]*

[1]Yonsei University Health System, Seoul, Republic of Korea; [2]Department of Biostatistics, Yonsei University, Seoul, Republic of Korea; and [3]Krannert Heart Institute, Indiana University, Indianapolis, IN, USA

Received 29 December 2010; accepted after revision 6 April 2011; online publish-ahead-of-print 15 May 2011

Background Although atrial fibrillation (AF) increases the risk of stroke, its relationship with atrial remodelling has not yet been studied. We hypothesized that the degree of electroanatomical remodelling of the left atrium (LA) is related to $CHADS_2/CHA_2DS_2VASc$ score and events of stroke.

Methods and results We compared $CHADS_2/CHA_2DS_2VASc$ score (0, 1, $\geq$2) or events of stroke with mean and regional LA volume [by three-dimensional (3D) computed tomography images] or LA endocardial voltage (by 3D-electroanatomical map) in 348 patients who underwent catheter ablation of AF (78.4% male, 55.4 $\pm$ 11.0 years old, paroxysmal AF:persistent AF = 215:133). We graded LA volume index as Grade 1 ($<$48.3 mL/m^2; $n = 80$), grade 2 (48.3–63.0 mL/m^2, $n = 82$), grade 3 (63.0–99.0 mL/m^2; $n = 94$), and grade 4 ($\geq$99.0 mL/m^2; $n = 92$). Results (i) The percentage volume of anterior portion of LA enlarged at the early stage of LA remodelling (Grade 1 vs. grade 2, $P = 0.006$) and the voltage of posterior venous LA was significantly reduced with the degree of LA remodelling ($P = 0.001$). (ii) Mean LA volume/body surface area (BSA), especially anterior portion of LA, was greater in patients with high $CHADS_2/CHA_2DS_2VASc$ score ($P = 0.002$). Mean LA voltage was significantly lower in patients with high CHA_2DS_2VASc score than low score ($P = 0.007$). (iii) In patients who experience stroke ($n = 22$), LA volume/BSA, especially anterior LA, was greater ($P = 0.012$), and LA endocardial voltage was lower ($P = 0.039$) than those without stroke.

Conclusion Electroanatomical remodelling of LA, estimated by LA volume and endocardial voltage, has significant relationship with the risk scores or events of stroke in patients with non-valvular AF.

Keywords Atrial fibrillation • $CHADS_2$ score • Stroke • Left atrium • Voltage

Introduction

Atrial fibrillation (AF) is the most common arrhythmia disorder, affecting up to 9% of the population by the age of 80 years, and is a significant risk factor for thromboembolic stroke.[1,2] $CHADS_2$ scores have been utilized as an excellent predictor of stroke and a guideline for anti-thrombotic therapy in patients with non-valvular AF.[3–5] Although the $CHADS_2$ score is an effective predictor of ischaemic stroke in patients with AF, the pathophysiologic mechanisms remain to be studied. Substrate or tissue factors related to $CHADS_2$ scores have to be considered. Recurrent fibrillatory activation of AF induces progressive electrical and tissue structural remodelling,[6–8] and reduction of left atrial (LA) endocardial voltage in the presence of fibrosis.[9] We previously reported that AF-related electroanatomical remodelling changes both entire and regional LA volume, endocardial voltage, conduction velocity, and distribution of complex fractionated atrial electrogram.[10–12] However, the relationship between the degree of

* Corresponding author: 250 Seungsanno, Seodaemun-gu, Seoul 120-752, Republic of Korea. Tel: +82 2 2228 58459; fax: +82 2 393 2041, Email: hnpak@yuhs.ac

electroanatomical remodelling and $CHADS_2$ score and the event of stroke has not yet been studied. Therefore, we hypothesized that the degree of electroanatomical remodelling of LA is related to $CHADS_2$ scores and to the event of stroke. The purposes of this study were to evaluate the regional volume change of LA depending on the degree of structural remodelling, and to compare the degree of mean and regional LA volume enlargement or LA endocardial voltage depending on $CHADS_2$ score and the events of stroke. We also compared the degree of electroanatomical remodelling with newly suggested risk scores for stroke in non-valvular AF—CHA_2DS_2VASc score.[13]

Methods

Patient selection

The study protocol was approved by the Institutional Review Board of our institute. All patients provided written informed consent. The study enrolled 348 patients with AF (male:female = 273:75, mean age = 55.4 ± 11.0 years old) who underwent radiofrequency catheter ablation (RFCA). Among them, 215 patients had paroxysmal AF, and 133 had persistent AF (PeAF). The exclusion criteria were as follows: (i) permanent AF refractory to the electrical cardioversion; (ii) LA sizes >55 mm measured on echocardiogram; (iii) AF with rheumatic valvular disease; (iv) associated structural heart disease other than left ventricular (LV) hypertrophy; (v) prior AF ablation; and (vi) sinus rhythm not maintained for LA voltage mapping before RFCA. The patients with the presence of an LA thrombus were excluded by transoesophageal echocardiography. We imaged all patients with a three-dimensional (3D) spiral computed tomography (CT) (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Amsterdam, Netherlands) to visually define the anatomy of LA and pulmonary veins (PVs). Trans-thoracic echocardiography was performed in every patient and LV systolic and diastolic functions were measured by ejection fraction (EF) and mitral valve area tissue Doppler (*E*/*E*'), respectively.

Electrophysiological mapping procedure

Intracardiac electrograms were recorded using the Prucka CardioLab™ Electrophysiology system (General Electric Medical Systems Inc., Easton Turnpike, Fairfield, USA), and catheter ablation procedures were performed on all patients using 3D electroanatomical mapping (NavX, St Jude Medical Inc., Minnetonka, MN, USA) merged with 3D spiral CT. Before catheter ablation, we generated an LA 3D electroanatomical map and a voltage map by obtaining contact bipolar electrograms from 350–400 points of the LA endocardium, during atrial pacing with a pacing cycle length of 500 ms. Bipolar electrograms were filtered from 32 to 300 Hz. Colour-coded voltage maps were generated by recording bipolar electrograms and measuring peak-to-peak voltage. The acquisition of an LA voltage map was abandoned if frequently re-initiating AF required electrical cardioversion more than three times. Only patients for whom the LA voltage map was available were included in the study.

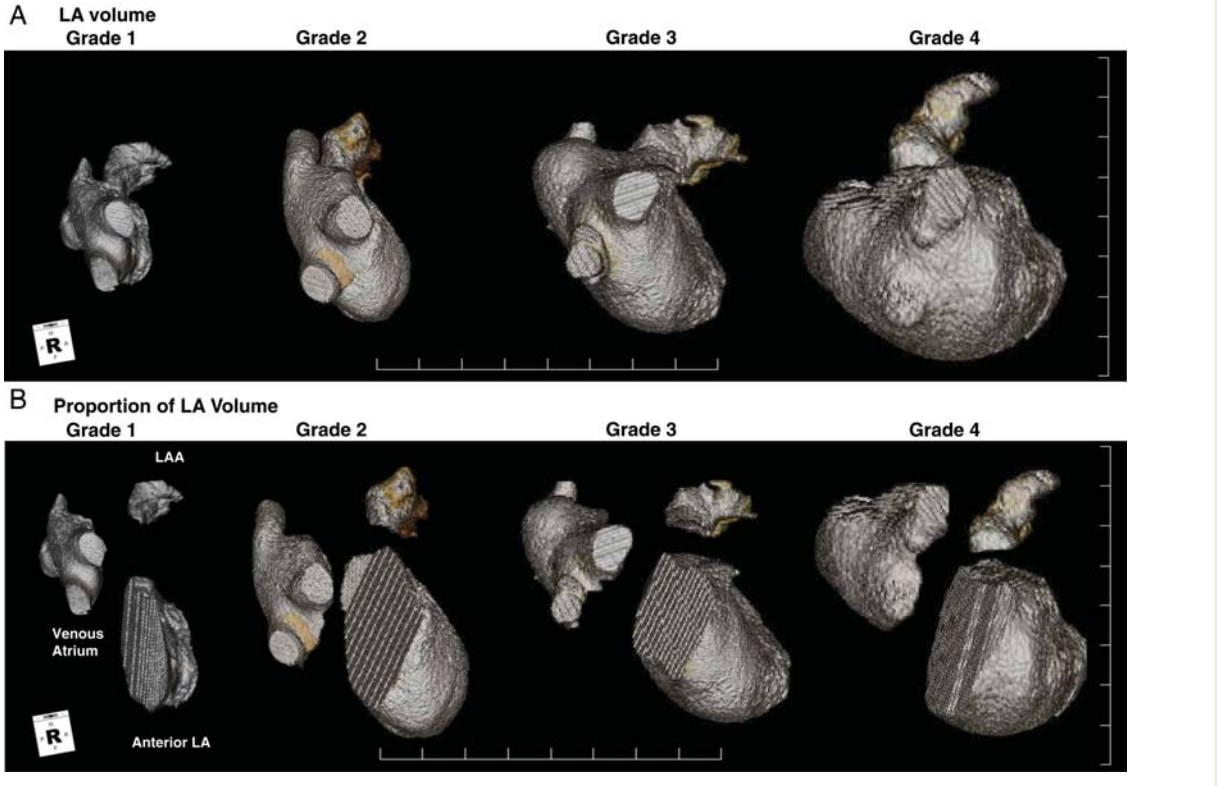

Figure 1 (*A*) Right lateral views of left atrium in the reconstructed three-dimensional spiral computed tomography image depending on the degree of left atrial remodelling. (*B*) left atrium images were divided into the venous atrium, the anterior left atrium, and the left atrial appendage. Volumetric measurement reveals significantly higher relative volume of the anterior left atrium in Stage 2 remodelling than in Stage 1.

Table 1 Comparison ofleft atrial morphology and left ventricular function according to atrial fibrillation -related left atrial size

	Grade 1 ($n = 87$)	Grade 2 ($n = 87$)	Grade 3 ($n = 87$)	Grade 4 ($n = 87$)	ANOVA *P* value	ANOVA Power
LA volumes (mL)						
Entire LA volume	74.9 ± 13.7	101.2 ± 12.1*	128.2 ± 13.7**†	170.8 ± 36.4§‡□	$P < 0.001$	1
Anterior LA volume	42.4 ± 10.5	60.6 ± 12.8*	78.6 ± 11.2**†	104.4 ± 28.7§‡□	$P < 0.001$	1
Venous LA volume	26.1 ± 8.2	32.3 ± 6.6*	38.8 ± 8.2**†	52.4 ± 15.0§‡□	$P < 0.001$	1
LAA volume	6.5 ± 3.1	8.7 ± 3.3	10.8 ± 3.6**†	14.0 ± 5.4§‡□	$P < 0.001$	1
Relative volumes of regional LA (%)						
Anterior LA volume	56.4 ± 8.5	59.5 ± 7.5	61.3 ± 5.4**	60.7 ± 8.0§	$P < 0.001$	0.979
Venous LA volume	34.9 ± 8.4	31.9 ± 7.4	30.2 ± 5.3**	31.0 ± 7.5§	$P < 0.001$	0.974
LAA volume	8.7 ± 3.9	8.6 ± 3.2	8.5 ± 3.1	8.3 ± 2.8	$P = 0.797$	0.094
LA voltage (mV)						
Mean LA voltage	1.6 ± 0.8	1.4 ± 0.6	1.3 ± 0.6	1.0 ± 0.6§	$P = 0.002$	0.873
Anterior LA voltage	1.4 ± 0.6	1.2 ± .0.6	1.3 ± 0.6	0.9 ± 0.6§	$P = 0.034$	0.878
Venous LA voltage	1.8 ± 1.3	1.0 ± 0.9*	1.1 ± 1.0**	0.8 ± 0.8§	$P = 0.001$	1
LAA voltage	3.1 ± 1.7	2.8 ± 1.5	2.5 ± 1.6	2.0 ± 1.3§	$P = 0.018$	0.708
LV function						
LVEF (%)	61.0 ± 7.2	60.9 ± 7.4	60.1 ± 8.2	57.2 ± 10.8§‡	$P = 0.012$	0.806
E/E'	8.5 ± 2.6	9.2 ± 3.6	9.7 ± 4.1	10.6 ± 4.4§	$P = 0.014$	0.781
Hypertension	26 (29.9 %)	38 (43.7 %)	47 (54.0 %)**	45 (51.7 %)§	$P = 0.005$	1
Renal insufficiency	2 (2.3 %)	1 (1.1 %)	2 (2.3 %)	1 (1.1 %)	$P = 0.880$	1
Recurrence	11 (12.6 %)	11 (12.6 %)	16 (18.4 %)	24 (27.6 %)§	$P = 0.005$	1

BSA, body surface area; LAA, LA appendage; LV, left ventricle; EF, ejection fraction, ANOVA, analysis of variance.
*$P < 0.05$, Grade 1 vs. Grade 2, **$P < 0.05$, Grade 1 vs. Grade 3, §$P < 0.05$, Grade 1 vs. Grade 4, †$P < 0.05$, Grade 2 vs. Grade 3, ‡$P < 0.05$, Grade 2 vs. Grade 4, □$P < 0.05$, Grade 3 vs. Grade 4.

Volumetric and curvilinear analyses of three-dimensionalspiral computed tomography imaging

The 3D spiral CT images of LA were analysed on an imaging processing workstation (Aquarius, Terarecon Inc., San Mateo, CA, USA) as described before.[11] The curvilinear lengths on LA were measured at the linear ablation sites: bilateral antral ablation line, roof line, posterior inferior line, left lateral isthmus line, anterolateral line, and anteroseptal line. Each LA image was divided into portions by embryological origin as follows: the venous LA (posterior LA including the antrum and posterior wall), LA appendage (LAA), and anterior LA (excluding the LAA and venous LA).[14] Although both LAA and anterior LA are embryologically of primordial atrial origin, they differ in geometry, myocardial fibre orientations, and distribution of autonomic innervations. Therefore, we divided LAA and anterior LA, and referenced them to the points of inflection on the 3D spiral CT image. The absolute and relative volumes of each portion were calculated and compared.

Off-line analyses of colour-coded three-dimensional maps of left atriums

We analysed colour-coded voltage maps of both anterior–posterior (AP) and posterior–anterior views that had been converted to image files as previously reported.[11] PVs were not included in the analysis. The digital measurements of colour-coded voltage maps were performed by a single student, using a consistent method, who was blinded to the clinical information of the maps. The percentage of colour-coded areas in each quadrant of the voltage maps was analysed by customized software (Image Pro, Silver Spring, MD, USA), and referenced to the colour scale bars. NavX detected peak-to-peak voltage differences of each contact bipolar electrogram, and changed them to colour codes. Low-voltage areas, defined as LA voltage ≤0.2 mV, were coded grey; high-voltage areas (>5.0 mV) were coded purple. The mean LA voltage was calculated by summation of % area of each colour multiplied by representative voltage, and then divided by the total area of LA. The reference distance was measured by the inter-electrode distances of coronary sinus catheters (duodecapolar catheter, St Jude Medical Inc.).

Data analyses

We classified patients according to $CHADS_2$ scores (0, $n = 154$; 1, $n = 124$; and ≥2, $n = 70$), CHA_2DS_2VASc score (0, $n = 146$; 1, $n = 106$; and ≥2, $n = 96$), the quartiles of 3D spiral CT measured LA volume index (Grade 1 ≤48.3 mL/m^2, $n = 87$; Grade 2, 48.3–63.0 mL/m^2, $n = 87$; Grade 3, 63.0–99.0 mL/m^2, $n = 87$; and Grade 4 ≥ 99.0 mL/m^2, $n = 87$), and the patients with ($n = 22$) or without ($n = 326$) stroke. We compared them by absolute or relative volumes or curvilinear lengths adjusted by BSA, mean LA voltage, LV systolic and diastolic function, and duration of AF. Data are expressed as the mean ± standard deviation. The statistical significance of these comparisons was assessed

using the Student *t*-test and analysis of variance (ANOVA) test. A *P* value of <0.05 was considered statistically significant.

Results

Enlargement of the anterior portion of left atrium in the early stages of left atrial remodelling

Figure 1 displays the right anterior oblique views of 3D spiral CT image of LA in each grade of remodelling. In Grade 2 LA remodelling, the anterior portion of the LA was remarkably enlarged, and the AP diameter of LA prolonged significantly. In contrast, the posterior venous LA and LAA were proportionally enlarged at Grade 3–4 of LA remodelling. *Table 1* summarizes LA volumes, regional lengths, endocardial LA voltage, LV functions, and recurrence. The proportion of relative volumes of anterior LA was significantly greater ($P < 0.001$), but posterior venous LA was smaller ($P < 0.001$) in patients with high-grade remodelling than those with low-grade remodelling (*Figure 2A*). The increase in relative anterior LA volume was more significant in Grade 2 than in Grade 1 remodelling ($P = 0.006$, *Figure 2A*). Left atrial endocardial voltage was generally reduced more in patients with high-grade remodelling than in those with low-grade remodelling ($P = 0.002$), and it was most significant in venous LA ($P = 0.001$, *Figure 2D*).

Greater left atrial volume in patients with higher $CHADS_2$ score

We compared mean and regional LA volumes in terms of $CHADS_2$ score (0, $n = 154$; 1, $n = 124$; and ≥ 2, $n = 70$; *Table 2*) and CHA_2DS_2VASc score (0, $n = 146$; 1, $n = 106$; and ≥ 2, $n = 96$; *Table 3*). Mean LA volume/BSA was significantly higher in patients with high $CHADS_2$ score ($P = 0.002$, *Figure 2B*), and this difference was significant especially in the regional volume of the anterior portion of LA ($P = 0.048$, *Table 2*). The proportions of PeAF were 34.4% in $CHADS_2$ score 0, 40.3% in $CHADS_2$ score 1, and 42.9% in $CHADS_2$ score ≥ 2 ($P =$ NS). In addition, EF was significantly lower ($P = 0.005$), *E/E'* was higher ($P = 0.002$), and the proportions of hypertension ($P < 0.001$) and renal insufficiency ($P = 0.016$) were higher in patients with higher $CHADS_2$ score than those with lower $CHADS_2$ score in ANOVA analyses (*Table 2*). When we compared depending on CHA_2DS_2VASc score (*Table 3*), these findings were consistent with the $CHADS_2$ scores, and LA volume/BSA was significantly higher in patients with high CHA_2DS_2VASc scores (*Figure 2C*). In the analyses of LA endocardial voltage, the mean and regional endocardial voltages tended to be lower in patients with high $CHADS_2$ score

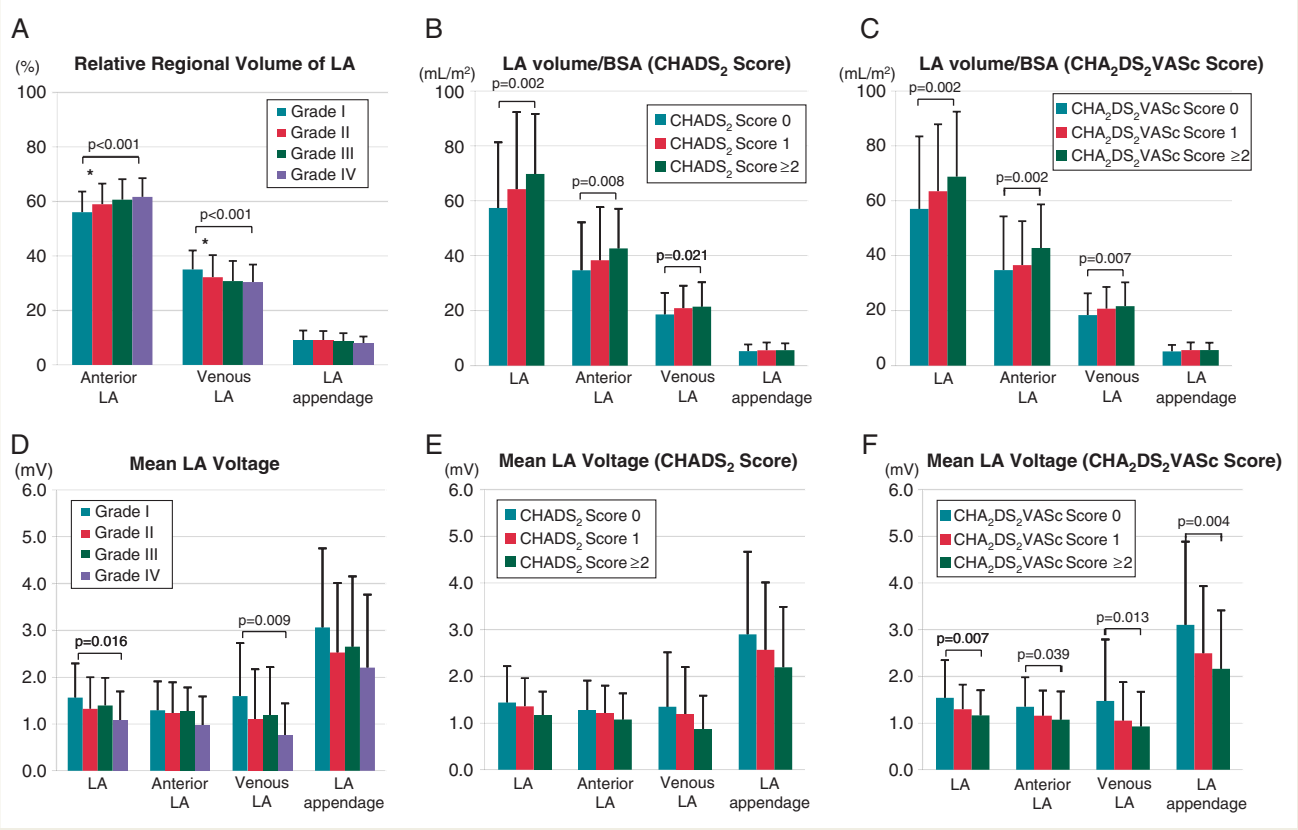

Figure 2 In high-grade remodelled left atrium, portion of anterior left atrium (*A*) was significantly larger, mean left atrium voltage (*D*) was significantly lower than those low-grade remodelled left atrium. In higher $CHADS_2$ score, left atrium volume/body surface area (*B*) was significantly larger; left atrium voltage (*E*) was lower than those lower $CHADS_2$ score. In higher CHA_2DS_2VASc score, left atrium volume/body surface area (*C*) was significantly larger; left atrium voltage (*F*) was significantly lower than in the case of lower $CHADS_2$ score.

Table 2 Comparison of left atrial morphology and left ventricular function according to atrial fibrillation -related $CHADS_2$ score

	$CHADS_2$ score 0 ($n = 154$)	$CHADS_2$ score 1 ($n = 124$)	$CHADS_2$ score ≥2 ($n = 70$)	ANOVA *P* value	ANOVA POWER
LA volumes/BSA (mL/m^2)					
Entire LA volume	57.4 ± 23.9	64.3 ± 28.1	69.8 ± 21.9**	$P = 0.002$	0.882
Anterior LA volume	34.7 ± 17.5	38.4 ± 19.4	42.7 ± 14.4**	$P = 0.008$	0.797
Venous LA volume	18.7 ± 7.9	20.9 ± 8.2	21.5 ± 8.9	$P = 0.021$	0.671
LAA volume	5.3 ± 2.5	5.6 ± 2.9	5.6 ± 2.5	$P = 0.520$	0.140
Relative volumes of regional LA (%)					
Anterior LA volume	58.3 ± 8.6	60.3 ± 6.5	60.5 ± 7.1	$P = 0.048$	0.599
Venous LA volume	32.9 ± 6.9	31.2 ± 6.9*	31.3 ± 6.3	$P = 0.111$	0.444
LAA volume	8.7 ± 3.3	8.5 ± 3.2	8.2 ± 3.3	$P = 0.555$	0.142
LA voltage (mV)					
Mean LA voltage	1.4 ± 0.8	1.4 ± 0.6	1.2 ± 0.5	$P = 0.110$	0.288
Anterior LA voltage	1.3 ± 0.6	1.2 ± 0.6	1.1 ± 0.6	$P = 0.285$	0.292
Venous LA voltage	1.3 ± 1.2	1.2 ± 1.0	0.9 ± 0.7	$P = 0.080$	0.388
LAA voltage	2.9 ± 1.8	2.6 ± 1.4	2.2 ± 1.3	$P = 0.077$	0.493
LV function					
LVEF (%)	61.2 ± 5.9	57.9 ± 9.5*	59.4 ± 10.7	$P = 0.005$	0.817
E/E'	8.9 ± 3.3	9.4 ± 3.4	10.3 ± 5.0**	$P = 0.002$	0.535
Hypertension	0 (0.0 %)	99 (79.8 %)*	57 (81.4 %)**	$P < 0.001$	1.000
Renal insufficiency	1 (0.6 %)	1 (2.4 %)	4 (5.7%)**	$P = 0.016$	1.000
Recurrence	23 (14.9 %)	30 (24.2 %)*	9 (12.9 %)	$P = 0.359$	0.882

BSA, body surface area; LAA, LA appendage; LV, left ventricle; EF, ejection fraction, ANOVA, analysis of variance.
*$P < 0.05$, $CHADS_2$ score 0 vs. $CHADS_2$ score 1, **$P < 0.05$, $CHADS_2$ score 0 vs. $CHADS_2$ score ≥2.

than in those with low scores (*Figure 2E*), but it was significant in terms of CHA_2DS_2VASc score ($P = 0.007$, *Figure 2F*).

Low left atrial endocardial voltage and higher anterior left atrial volume in patients with stroke

Figure 3A and *B* display the representative examples of CT-merged LA voltage maps, and the patients who experienced stroke show low endocardial voltage with enlarged LA volume in comparison with the patient without stroke. We compared them with 326 patients without stroke and summarized this in *Table 4*. There were 22 patients who experienced episodes of stroke in this study. The stroke occurred 18.2 ± 18.4 months before catheter ablation, and CHADS2 score was 3.2 ± 0.2 at that time. The type of stroke was ischaemic embolic stroke in all 22 patients, but haemorrhagic transformation occurred during stroke management in 2 patients. In patients who had experienced a previous stroke, mean LA volume/BSA ($P = 0.012$), especially anterior LA ($P = 0.006$), was significantly enlarged, and mean LA endocardial voltage ($P = 0.039$), especially venous LA voltage ($P = 0.005$), was significantly lower than those without stroke (*Figure 3C* and *D*). In the uni-variate analyses (*t*-test), LA diameter ($P = 0.011$), left ventricular ejection fraction (LVEF; $P = 0.041$), $CHADS_2$ score ($P < 0.001$), LA volume/BSA ($P = 0.026$), LAA volume% ($P = 0.012$), anterior LA volume% ($P = 0.025$), and LA voltage ($P = 0.039$) were related with the event of stroke. In the multi-variate regression analysis, the factor most related to the episode of stroke was $CHADS_2$ score (OR = 3.641, CI 2.033–6.521, $P < 0.001$) among them.

Discussion

This is the first study that reports on the relationship between the degree of electroanatomical remodelling of LA and the risk or events of stroke in patients with non-valvular AF. We also elucidated disproportional enlargement of the anterior portion of LA in the early stages of structural remodelling and its relationship with $CHADS_2$ score, and low endocardial voltage of posterior venous atrium in patients with stroke. Therefore, $CHADS_2$ score represents not only a clinical risk factor for ischaemic stroke, but is also related to atrial substrates for thoromboembolism in patients with AF.

Risks scores and potential mechanisms of stroke in patients with non-valvular atrial fibrillation

Atrial fibrillation causes a five-fold increase in the risk of ischaemic stroke or transient ischaemic attack (TIA).[15] $CHADS_2$ score is a risk stratification scheme for ischaemic stroke in patients with non-valvular AF based on the presence of heart failure,

Table 3 Comparison of left atrial morphology and left ventricular function according to atrial fibrillation-related $CHADS_2VASc$ score

	CHA_2DS_2VASc score 0 ($n = 146$)	CHA_2DS_2VASc score 1 ($n = 106$)	CHA_2DS_2VASc score ≥2 ($n = 96$)	ANOVA *P* value	ANOVA POWER
LA volumes/BSA (mL/m^2)					
Entire LA volume	57.1 ± 26.4	63.5 ± 24.4	68.8 ± 23.7**	$P = 0.002$	0.885
Anterior LA volume	34.8 ± 19.6	36.6 ± 16.0	42.8 ± 15.9**†	$P = 0.002$	0.873
Venous LA volume	18.4 ± 8.0	20.7 ± 7.9*	21.7 ± 8.7**	$P = 0.007$	0.810
LAA volume	5.2 ± 2.4	5.6 ± 2.8	5.7 ± 2.7	$P = 0.256$	0.269
Relative volumes of regional LA (%)					
Anterior LA volume	58.3 ± 8.5	59.6 ± 6.9	61.1 ± 6.8**	$P = 0.019$	0.701
Venous LA volume	33.0 ± 8.3	31.8 ± 6.8	30.7 ± 6.6	$P = 0.050$	0.553
LAA volume	8.7 ± 3.3	8.6 ± 3.1	8.2 ± 3.4	$P = 0.525$	0.170
LA voltage (mV)					
Mean LA voltage	1.5 ± 0.8	1.3 ± 0.5	1.2 ± 0.5**	$P = 0.007$	0.587
Anterior LA voltage	1.3 ± 0.6	1.2 ± 0.5	1.1 ± 0.6**	$P = 0.039$	0.332
Venous LA voltage	1.5 ± 1.3	1.1 ± 0.8	0.9 ± 0.7**	$P = 0.013$	0.816
LAA voltage	3.1 ± 1.8	2.5 ± 1.4	2.2 ± 1.3**	$P = 0.004$	0.811
LV function					
LVEF (%)	60.6 ± 6.9	57.3 ± 9.8*	61.5 ± 9.0†	$P = 0.001$	0.924
E/E'	9.0 ± 3.4	8.8 ± 3.2	11.0 ± 4.5**†	$P < 0.001$	0.968
Hypertension	0 (0.0%)	80 (75.2%)*	76 (79.2%)**	$P < 0.001$	1.000
Renal insufficiency	0 (0.0%)	2 (1.9%)	4 (4.2%)	$P = 0.051$	1.000
Recurrence	24 (16.4%)	21 (19.8%)*	17 (17.7%)	$P = 0.683$	1.000

BSA, body surface area; LAA, LA appendage; LV, left ventricle; EF, ejection fraction, ANOVA, analysis of variance.
*$P < 0.05$, $CHADS_2$ score 0 vs. $CHADS_2$ score 1, **$P < 0.05$, $CHADS_2$ score 0 vs. $CHADS_2$ score ≥2, †$P < 0.05$, $CHADS_2$ score 1 vs. $CHADS_2$ score ≥2.

hypertension, age >75 years old, diabetes, previous stroke, or TIA.[16] The 2006 version of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines/European Society of Cardiology Committee for Practice (ACC/AHA/ESC) practical guidelines for AF recommends warfarin or aspirin for patients depending on their $CHADS_2$ score.[5] Recently, European Society of Cardiology have suggested new guidelines for AF management,[13] and proposed a CHA_2DS_2-VASc score that strengthens the importance of age, sex, and combined vascular disease as risk factors for ischaemic stroke in addition to $CHADS_2$ score. Although both $CHADS_2$ and CHA_2DS_2VASc scores are effective predictors for ischaemic stroke, their pathophysiologic mechanisms remain to be clarified. Atrial contractile remodelling and blood stasis in LA during AF has generally been considered to be a major mechanism of thromboembolism in patients with AF.[17–19] Blood stasis or hypercoagulable states are major contributors for thrombogenesis, but tissue factors cannot be underestimated. $CHADS_2$ score and CHA_2DS_2VASc score include risk factors related to vascular remodelling, metabolic syndrome, change of cardiac substrates, or tissue factors. The degree of electroanatomical remodelling of AF is closely related with myocardial fibrosis,[20,21] matrix remodelling, and angiotensin II-NADPH oxidase-mediated thrombus formation.[22] In this study, we demonstrated the relationship between LA volume/endocardial voltage and risk scores or events of stroke in patients with AF.

Electroanatomical remodelling process in atrial fibrillation

The mechanisms for LA remodelling include pressure or volume overload to LA by LV dysfunction, deranged plasma volume control, intensified neurohormonal activation, or atriomyopathy itself.[23] In this study, the anterior portion of the LA was enlarged in the early stages of LA remodelling, and the potential mechanisms are as follows: first, haemodynamic overload may stretch thin the traveculated wall of the anterior portion of LA early by Laplace's law. Secondly, the posterior venous LA and the anteroseptum abut the fixed rigid structures, the spine, and the ascending aorta, respectively. Therefore, LA volume increased anterolaterally and the volume of anterior LA was enlarged in the early phases of remodelling.

The presence of fibrosis/low-voltage tissue has been postulated as a potential cause of abnormalities in atrial activation that may underlie the initiation and maintenance of fibrillation.[24,25] The degree of voltage reduction may help grade the severity of tissue pathology underlying AF before and after catheter ablation.[26] Increased fibrosis has also been clearly demonstrated in human LA tissue specimens of patients with AF,[20,21] and correlations have been observed between serum markers of atrially selective fibroblasts and clinical AF.[27] We also previously reported that low endocardial voltage of LA is closely related to LA volume remodelling,[11] reduced conduction velocity,[10] and the patterns of

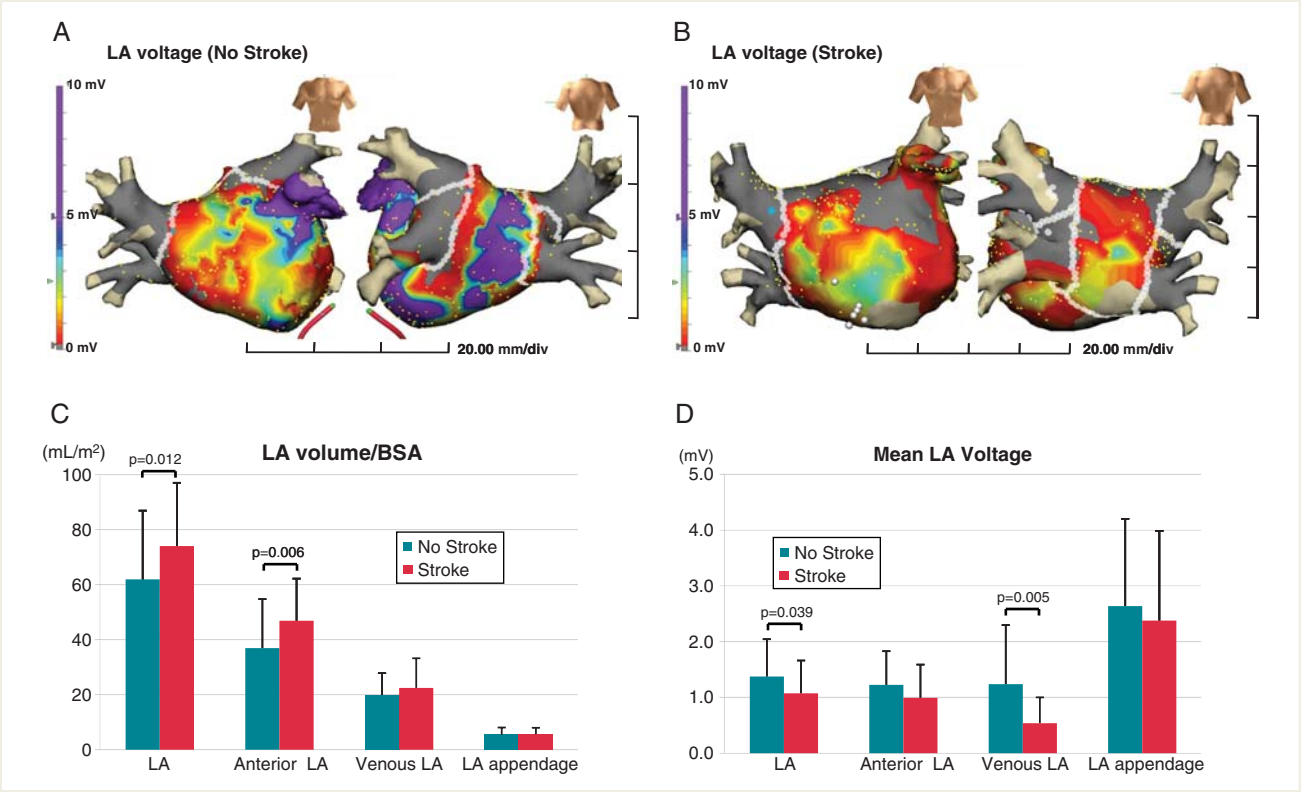

Figure 3 Anterior and posterior views of colour-coded left atrium voltage map during ablation. (*A*) High left atrium voltage in patients without stroke. (*B*) Low left atrium voltage in patients with stroke. In patients with stroke, mean left atrium volume and relative regional volume of anterior left atrium were larger (*C*), and mean left atrium voltage and regional left atrium voltage of venous atrium were lower (*D*) than those without stroke.

complex fractionated atrial electrograms in AF.[12] In this study, the degree of electroanatomical remodelling of LA was directly related to the risk or events of stroke in patients with AF. Further studies by non-invasive imaging methods, such as fibrosis on magnetic resonance imaging or stain on echocardiography, will characterize the degree of LA remodelling anatomically and functionally.[28]

Clinical implication of left atrial structural remodelling

Electroanatomical remodelling of the atria has been known to be a predictor of AF recurrence after cardioversion[29] or RFCA,[11,30] and a risk of stroke, as shown in this study. Therefore, more strict anti-coagulation is warranted in those patients with low-voltage scars and enlarged LA. Longer duration of RF energy delivery is more of a necessity for effective rhythm control in AF patients with remodelled atria than for those with less remodelled atria. However, the operator should keep in mind that profuse RF ablation can increase LA scar or atriomyopathy,[26] and might raise the risk of stroke by electroanatomical remodelling. Whether reverse remodelling and LA voltage occurs after successful catheter ablation of AF is unclear. The appropriate strategy for anti-coagulation after abolishing AF remains to be studied. New drugs[31,32] or devices[33] provide more options for AF management, and customized guidelines will be required according to the symptoms, haemodynamic factors, and risks of stroke.

Study limitations

The patients included in this study were a highly selective group referred for RFCA, and the number of patients was also limited. We also excluded patients with LA size of >50 mm. Because we acquired voltage maps via point-by-point contact mapping, the maps did not reflect a spatiotemporally homogeneous distribution. We analysed 3D voltage maps using 2D measurements. Although we strictly followed ACC/AHA/ESC guideline based on the $CHADS_2$ score,[5] we do not have data of the anti-thrombotic regimen at the time of ischaemic stroke because most patients included in this study were referred patients for catheter ablation. The patient group in this study was highly selected patients with relatively small LA volume with low risk of stroke. Therefore, the result of this study may not be extrapolated to the patients with permanent AF and significant LA remodelling.

Conclusion

We documented different patterns of $CHADS_2$ score in patients with structurally remodelled LA. In patients with non-valvular AF, LA volume was larger in patients with high $CHADS_2$ score than

Table 4 Degree of left atrial remodelling in patients with and without stroke

	No stroke ($n = 326$)	Stroke ($n = 22$)	*P* value
LA volumes/BSA (mL/m^2)			
Entire LA volume	61.5 ± 25.5	74.1 ± 23.0	$P = 0.012$
Anterior LA volume	36.9 ± 17.8	46.9 ± 15.3	$P = 0.006$
Venous LA volume	19.8 ± 8.0	22.5 ± 10.8	$P = 0.074$
LAA volume	5.4 ± 2.6	5.7 ± 2.3	$P = 0.329$
Relative volumes of regional LA (%)			
Anterior LA volume	59.3 ± 7.6	62.2 ± 8.0	$P = 0.044$
Venous LA volume	32.1 ± 7.4	30.6 ± 7.6	$P = 0.185$
LAA volume	8.6 ± 3.3	7.2 ± 2.1	$P = 0.025$
LA voltage (mV)			
Mean LA voltage	1.4 ± 0.7	1.1 ± 0.6	$P = 0.039$
Anterior LA	1.2 ± 0.6	1.0 ± 0.6	$P = 0.068$
Venous LA	1.2 ± 1.1	0.5 ± 0.5	$P = 0.005$
LAA	2.6 ± 1.6	2.4 ± 1.6	$P = 0.259$
LV function			
LVEF (%)	59.6 ± 8.6	63.0 ± 8.1	$P = 0.041$
E/E'	9.4 ± 3.8	10.5 ± 3.2	$P = 0.120$
Hypertension	144 (44.2%)	12 (54.5%)	$P = 0.216$
Renal insufficiency	6 (1.8%)	0 (0.0%)	$P = 0.673$
Recurrence	62 (19.0%)	0 (0.0%)	$P = 0.041$

BSA, body surface area; LAA, LA appendage; LV, left ventricle; EF, ejection fraction.

those with low $CHADS_2$ score and LA voltage was lower in patients with stroke. Thus, stroke risk factors may be related to the degree of electroanatomical remodelling of LA and anterior LA might play a role in the early phase of structural remodelling in patients with AF.

Funding

This work was supported by a grant (A085136) from the Korea Health 21 R&D Project, the Ministry of Health and Welfare, and a grant (2010-0010537) from the Basic Science Research Program run by the National Research Foundation of Korea (NRF), which is funded by the Ministry of Education, Science and Technology of the Republic of Korea.

Conflict of interest: none declared.

References

1. Page RL. Clinical practice. Newly diagnosed atrial fibrillation. *N Engl J Med* 2004; **351**:2408–16.
2. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359–64.
3. Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM *et al.* Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003;**290**:2685–92.
4. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. *Am Heart J* 2008;**156**:57–64.
5. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA *et al.* ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the management of patients with atrial fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;**114**:e257–354.
6. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;**54**:230–46.
7. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997; **96**:1180–4.
8. Ausma J, Litjens N, Lenders MH, Duimel H, Mast F, Wouters L *et al.* Time course of atrial fibrillation-induced cellular structural remodeling in atria of the goat. *J Mol Cell Cardiol* 2001;**33**:2083–94.
9. Boldt A, Wetzel U, Lauschke J, Weigl J, Gummert J, Hindricks G *et al.* Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. *Heart* 2004;**90**:400–5.
10. Park JH, Pak HN, Kim SK, Jang JK, Choi JI, Lim HE *et al.* Electrophysiologic characteristics of complex fractionated atrial electrograms in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2009;**20**:266–72.
11. Park JH, Pak HN, Choi EJ, Jang JK, Kim SK, Choi DH *et al.* The relationship between endocardial voltage and regional volume in electroanatomical remodeled left atria in patients with atrial fibrillation: comparison of three-dimensional computed tomographic images and voltage mapping. *J Cardiovasc Electrophysiol* 2009;**20**:1349–56.
12. Park JH, Park SW, Kim JY, Kim SK, Jeoung B, Lee MH *et al.* Characteristics of complex fractionated atrial electrogram in the electroanatomically remodeled left atrium of patients with atrial fibrillation. *Circ J* 2010;**74**:1557–63.
13. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S *et al.* Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**: 2369–429.
14. Douglas YL, Jongbloed MR, Gittenberger-de Groot AC, Evers D, Dion RA, Voigt P *et al.* Histology of vascular myocardial wall of left atrial body after pulmonary venous incorporation. *Am J Cardiol* 2006;**97**:662–70.
15. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;**22**:983–8.
16. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–70.
17. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for 'atrial stunning' as a mechanism of thromboembolic complications. *J Am Coll Cardiol* 1994;**23**:307–16.
18. Missault L, Jordaens L, Gheeraert P, Adang L, Clement D. Embolic stroke after unanticoagulated cardioversion despite prior exclusion of atrial thrombi by transoesophageal echocardiography. *Eur Heart J* 1994;**15**:1279–80.
19. Dunn MI, Marcum JL. Atrial mechanical performance following internal and external cardioversion of atrial fibrillation: its relationship to peripheral embolization and acute cerebrovascular accident. *Chest* 2002;**121**:1–3.
20. Kostin S, Klein G, Szalay Z, Hein S, Bauer EP, Schaper J. Structural correlate of atrial fibrillation in human patients. *Cardiovasc Res* 2002;**54**:361–79.
21. Nakai T, Chandy J, Nakai K, Bellows WH, Flachsbart K, Lee RJ *et al.* Histologic assessment of right atrial appendage myocardium in patients with atrial fibrillation after coronary artery bypass graft surgery. *Cardiology* 2007;**108**:90–6.
22. Goette A, Bukowska A, Lendeckel U, Erxleben M, Hammwohner M, Strugala D *et al.* Angiotensin II receptor blockade reduces tachycardia-induced atrial adhesion molecule expression. *Circulation* 2008;**117**:732–42.
23. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS *et al.* Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;**292**:2471–7.
24. Spach MS, Boineau JP. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias. *Pacing Clin Electrophysiol* 1997;**20**(Part 2):397–413.
25. Spach MS, Josephson ME. Initiating reentry: the role of nonuniform anisotropy in small circuits. *J Cardiovasc Electrophysiol* 1994;**5**:182–209.
26. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S *et al.* Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. *J Am Coll Cardiol* 2005; **45**:285–92.
27. Li X, Ma C, Dong J, Liu X, Long D, Tian Y, Yu R. The fibrosis and atrial fibrillation: is the transforming growth factor-beta 1 a candidate etiology of atrial fibrillation. *Med Hypotheses.* 2008;**70**:317–9.
28. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S *et al.* Left atrial strain and strain rate in patients with paroxysmal and persistent

atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. *Circ Cardiovasc Imaging* 2010;**3**:231–9.
29. Volgman AS, Soble JS, Neumann A, Mukhtar KN, Iftikhar F, Vallesteros A *et al.* Effect of left atrial size on recurrence of atrial fibrillation after electrical cardioversion: atrial dimension versus volume. *Am J Card Imaging* 1996;**10**:261–5.
30. Tsao HM, Wu MH, Huang BH, Lee SH, Lee KT, Tai CT *et al.* Morphologic remodeling of pulmonary veins and left atrium after catheter ablation of atrial fibrillation: insight from long-term follow-up of three-dimensional magnetic resonance imaging. *J Cardiovasc Electrophysiol* 2005;**16**:7–12.
31. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.
32. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C *et al.* Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668–78.
33. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M *et al.* Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–42.

IMAGES IN ELECTROPHYSIOLOGY

doi:10.1093/europace/eur237
Online publish-ahead-of-print 21 July 2011

A case of atrioventricular nodal reentrant tachycardia with high take-off coronary sinus

Seigo Yamashita, Teiichi Yamane*, and Michihiro Yoshimura

Department of Cardiology, The Jikei University School of Medicine, 3-25-8 Minato-ku Nishi-shinbashi, Tokyo 105-8461, Japan

* Corresponding author. Tel: +81 33 433 1111; fax: +81 33 433 1112. E-mail: yamanet1@aol.com

A 73-year-old female with atrioventricular nodal reentrant tachycardia (AVNRT) presented with high-takeoff coronary sinus (CS). Coronary sinus venography revealed that the CS ostium was located at an unusual site where the His-bundle is supposed to be located (arrows in *Figure 1A and B*), and the successful ablation site for the slow pathway was located below the CS ostium (*Figures 1*A–C). This patient was treated by slow-pathway ablation using only the electrophysiological approach. Therefore, slow pathway ablation for AVNRT should not be guided by only anatomical approaches in cases with an anomaly of the CS.

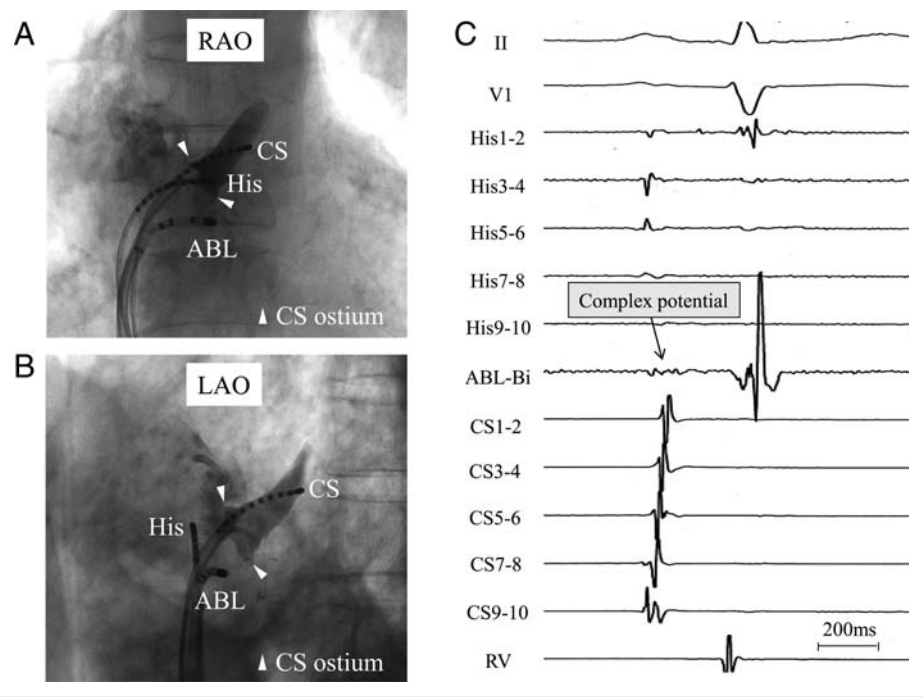

Figure 1 Radiographs demonstrating high-takeoff CS, and intracardiac electrogram.

Conflict of interest: none declared.